Attorney's Docket No.: 06666/149001/ USC 3106

REMARKS

Reconsideration and allowance of the above referenced application are respectfully requested.

Claims 1, 3 and 9-10 remain rejected as allegedly being anticipated by Hall et al. (PCT Application WO 98/44938). This contention is respectfully traversed, and it is respectfully suggested that the rejection does not meet the patent office's burden of providing a prima facie showing of unpatentability. Claim 1 requires a targeted retroviral vector particle with a modified viral surface protein. The modified viral surface protein has a von Willebrand of the factor collagen binding motif as well as a gene and where the site of the gene encodes GM-CSF. The rejection alleges that all of this is shown by Hall et al., and specifically alleges that the particle in Hall et al. can include GM-CSF. With all due respect, this is respectfully traversed.

Hall et al. does teach a vector particle which may be a retroviral vector particle. However, while Hall et al. teaches that the particle could include a therapeutic gene, this mere teaching by itself is certainly not sufficient to anticipate every specific gene ever considered. More specifically, Hall et al. fails to teach the limitation of a von Willebrand factor collagen binding motif and a gene encoding GM-CSF. Quite

CSF. Quite simply, this is not taught or suggested by Hall et al. The rejection states that the particle "is identical to the claimed targeted retroviral particle". This contention is again respectfully traversed. While Hall et al. does teach a retroviral particle, it does not teach the same specific retroviral particle as claimed. Since Hall et al. does not teach the same particle, the patent office has not met their burden of providing a prima facie showing of unpatentability. Therefore, the burden has not shifted to applicants to rebut this rejection, and the statement that applicants do not provide any evidence is respectfully suggested to be entirely beside the point. Hall et al. does not disclose the specific claimed subject matter.

Claims 1, 3 and 9-10 stand rejected as being unpatentable over Hall et al., or Hall et al.'s Human Gene Therapy article, or Liu et al., Gordon et al., in view of Kurane et al. and Borello et al. This contention is again respectfully traversed. With all due respect, there is no suggestion to combine the references. Even if combined, moreover, the hypothetical combinations still would not teach or suggest the claimed subject matter. With all due respect, the rejection is based on hindsight and not on the teaching of the references themselves.

The Primary References

Hall-1 (WO 98/44938)

Hall-1 teaches a viral vector particle having a modified viral surface protein wherein the viral surface protein is modified to include a targeting polypeptide including a binding region which binds to an extracellular matrix component. Hall-1 teaches a modified retroviral targeting polypeptide comprising the collagen-binding domain of von Willebrand factor. Hall-1 also teaches a therapeutic gene encoded by the viral particle, including a cytokine such as GM-CSF, and methods of delivery and treatment of diseases and disorders associated with exposed extracellular matrix components, including cancer. Hall-1 does not teach or suggest actively recruiting host mononuclear cells to the site of tumor as a result of expression of GM-CSF from cells of a tumor transduced by targeted retroviral particles comprising a modified surface protein for targeting to the extracellular matrix or tumor vasculature of a tumor and a gene encoding GM-CSF.

Hall-2 (Human Gene Therapy 11:983-993 (2000))

Hall-2 teaches retroviral vectors bearing chimeric envelope proteins comprised of von Willebrand factor-derived matrix-binding sequences capable of transducing cells resulting in expression of a reporter gene (□-galatosidase). Hall-2 teaches transduction of tumor foci (approximately 1-3%) as detected by

reporter gene expression after portal vein infusion of a matrix-targeted vector in a nude mouse model of liver metastasis. Hall-2 suggests that targeted injectable retroviral vectors would be suitable for improving therapeutic gene delivery in numerous clinical applications, including metastatic cancer. Hall-2 does not teach or suggest retroviral vectors encoding cytokines and modified surface proteins for targeting to extracellular matrix for transduction of tumors wherein host mononuclear cells are recruited to the site of the tumor upon expression of GM-CSF from transduced tumor cells.

Gordon et al.

Gordon et al. teaches inhibition of tumor growth via expression of cytocidal cyclin G1 in tumor cells transduced with retroviral vectors bearing chimeric envelope proteins comprising collagen-binding polypeptides for targeting to extracellular matrix components. Gordon et al. teaches antiproliferation of tumor cells resulting from cytocidal gene expression from transduced tumor cells. Gordon et al. does not teach or suggest reducing tumor mass by actively recruiting host mononuclear cells to the site of tumor in response to cytokine expression from cells of a tumor transduced by retroviral particles comprising modified surface proteins for targeting to extracellular matrix or tumor vasculature of a tumor and encoding a GM-CSF gene.

Liu et al.

Liu et al. teaches a retroviral vector particle comprised of surface proteins that incorporate tumor vasculature targeting motifs into moloney murine leukemia virus env escort proteins that enhance retrovirus binding and transduction of human endothelial cells. Liu et al. does not teach a retroviral particle comprising a modified surface protein including a von Willebrand factor collagen binding motif for targeting to tumor vasculature or extracellular matrix of a tumor to transduce cells of the tumor and actively recruit host mononuclear cells to the site of tumor in response to cytokines expressed from tumor cells transduced by the retroviral particle.

The Secondary References

As described in detail below, neither of the secondary references, alone or together, make up the defects in the primary references. The primary references do not teach or suggest recruitment of host mononuclear cells to the site of a tumor. The secondary references do not cure this defect.

Borrello et al.

Borrello et al. teaches generating a GM-CSF-producing bystander cell line for use in antitumor vaccine development. Borrello et al. teaches that delivering GM-CSF to the animal with a mixture of autologous tumor cells and the GM-CSF-producing bystander cells primes antitumor immune responses that

are equivalent or better than those achieved using autologous tumor cells directly transduced to secrete GM-CSF. Borrello et al. does not teach or suggest recruiting host mononuclear cells in response to GM-CSF expression from cells of a tumor transduced by targeted retroviral vectors comprising modified surface proteins for targeting to extracellular matrix components or tumor vasculature of a tumor and a gene encoding GM-CSF.

Kurane et al.

Kurane et al. teaches methods of delivering cytokines to an animal as an adjuvant for priming lymph node cells draining sites for vaccine inoculation for the purposes of generating immune cells for adoptive immunotherapy. Kurane et al. teaches that local delivery of GM-CSF by autocrine or paracrine secretion of genetically engineered cells, as well as direct intratumoral delivery was capable of enhancing the antitumor reactivity of vaccine-primed lymph node cells as compared to systemic administration, which did not. Kurane et al. does not teach actively recruiting host mononuclear cells to the site of tumor in response to GM-CSF expression from cells of a tumor transduced by retroviral particles comprising a modified surface protein for targeting to extracellular matrix or tumor vasculature of a tumor and encoding a GM-CSF gene.

The combination of teachings of the cited references does not result in any of the instantly claimed elements

The Examiner has rejected claims 1, 3, 9 and 10 as being obvious to an artisan of skill to modify the vector(s) of Hall-1, Hall-2, Liu et al, and Gordon et al. by cloning the GM-CSF encoding sequences taught by Borrello et al. with reasonable expectation of success and use the resultant vector for delivering GM-CSF to a tumor in an animal.

As described in detail above, none of the references alone or in combination teach or suggest recruitment of host mononuclear cells to the site of tumor in an animal in response to GM-CSF expression from cells of a tumor transduced by targeted retroviral particles as instantly claimed.

As indicated by the Examiner in the Final Office Action dated December 28, 2004, "Applicants arguments that expression of GM-CSF at tumor locations resulted in reduced tumor mass". The Examiner indicates that the arguments were found unpersuasive as being irrelevant to the pending claims. The Examiner then states: "...applicants have argued of un-expected result of recruitment of host mononuclear cells to the site of tumor. It is noted that this result is irrelevant to the instantly presented claims because no such limitation is recited in the claims."

As amended herein, Claim 1 now recites "recruitment of host mononuclear cells to the site of the tumor." The instant claims thus provide for a retroviral particle comprising a modified surface protein for targeting to extracellular matrix or tumor vasculature of a tumor and encoding a GM-CSF gene for transduction of cells of a tumor, wherein expression of GM-CSF results in the recruitment of host mononuclear cells to the site of the tumor, when the retroviral particle is administered to a subject as a pharmaceutical composition in an effective amount for the treatment of cancer. As indicated by the Examiner, experiments performed by the Applicants demonstrating the recruitment of host mononuclear cells to the site of tumor after transduction with the instantly claimed targeted retroviral particles was "un-expected". Therefore, following the teachings of the references alone or in combination would not result in the elements as instantly claimed. Therefore, the instant claims are not obvious over the teachings of the cited references.

The combination of teachings does not result in the instantly claimed subject matter that includes the element of host mononuclear cell recruitment to the site of tumor in response to GM-CSF expression from cells of a tumor transduced by the instantly claimed retroviral particles. None of the cited art teaches, suggests or mentions a retroviral particle

targeted to extracellular matrix or tumor vasculature of a tumor encoding a gene for GM-CSF for transduction of tumor cells to recruit host mononuclear cells to the site of tumor for the treatment of cancer. The rejection of claims 1, 3, 9, and 10 as being unpatentable under 35 U.S.C. §103(a) in view of the cited references is respectfully traversed.

It is believed that all of the pending claims have been addressed in this paper. However, failure to address a specific rejection, issue or comment, does not signify agreement with or concession of that rejection, issue or comment. In addition, because the arguments made above are not intended to be exhaustive, there may be reasons for patentability of any or all pending claims (or other claims) that have not been expressed. Finally, nothing in this paper should be construed as an intent to concede any issue with regard to any claim, except as specifically stated in this paper, and the amendment of any claim does not necessarily signify concession of unpatentability of the claim prior to its amendment.

Applicants ask that all claims be allowed. Please apply the one month extension of time fee in the amount of $60, and

any other applicable charges or credits, to Deposit Account No. 06-1050.

Respectfully submitted,

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